Dr V. Bala Subramanian is supported by the British Heart Foundation. We acknowledge the technical assistance of Mrs Christagopoulos and the secretarial assistance of Mrs Jean Wright.

Requests for reprints should be addressed to V. B. S.

REFERENCES

1. Hoffmann P. Behandlung koronarer Durchblutungsstorungen mit Isoptin in der Praxis. *Mediz Klin* 1964; **59**: 1387–91.
2. Herxheimer A. Claims for Cordilox. *Drug Therap Bull* 1967; **5**: 85–87.
3. Phear DN. Verapamil in angina. *Br Med J* 1968; ii: 740–41.
4. Livesley B, Catley PF, Campbell RC, Oram S. Double blind evaluation of verapamil, propranolol and isosorbide dinitrate against a placebo in the treatment of angina pectoris. *Br Med J* 1973; ii: 375–78.
5. Nayler WG, McInnes I, Swann JB, et al. Some effects of iproveratril (Isoptin) on the cardiovascular system. *J Pharmaco Exp Ther* 1968; **161**: 247–61.
6. Nayler WG, Krikler D. Verapamil and the myocardium. *Postgrad Med J* 1974; **50**: 441–46.
7. Bala Subramanian V, Khanna PK, Hoon RS. On-line digital computer quantitated ST segment response to submaximal treadmill exercise. *J Assoc Physicians of India* 1975; **23(1)**: 1–8.
8. Bala Subramanian V, Khanna PK, Narayanan GR, Hoon RS. Quantified multistage treadmill exercise—a reliable method for testing antianginal drugs. *J Assoc Physicians of India* 1975; **23**: 597–601.
9. Bala Subramanian V. Assessment of antianginal drugs by serial treadmill exercise. In: MacFarlane PW, ed. Progress in Electrocardiology. Kent: Pitman Medical, 1979: 329–32.
10. Sheffield LT. Quantitative approach to exercise testing for ischæmic heart disease. In: Quantitation in Cardiology. Netherlands: Leiden University Press, 1972.
11. Prichard BNC. Propranolol in the treatment of angina: a review. *Postgrad Med J* 1976; **52**: 31–41.
12. Keyrilainen O, Uusitalo A. Effects of metoprolol in angina pectoris—a subacute study with exercise tests and a long term tolerability study. *Acta Med Scand* 1976; **199**: 491–97.
13. Ekelund LG, Anders G, Olsson ORO, Rossner S. Effects of the cardioselective beta adrenergic receptor blocking agent—metoprolol-in angina pectoris. A subacute study with exercise tests. *Br Heart J* 1976; **38**: 155–61.
14. Reichek N. Long-acting nitrates in the treatment of angina pectoris. *JAMA* 1976; **236**: 1399–1402.
15. Marshall A, Barritt DW, Roberts CJC. Raynaud's phenomenon as side effects of beta blocker. *Br Med J* 1976; ii: 301.
16. Rodger JC, Sheldon CD, Lerski RA, Livingstone WR. Intermittent claudication complicating beta blockade. *Br Med J* 1976; i: 1125.
17. Petrie JC, Galloway DB, Jeffers TA, Webster J. Adverse reactions to beta blocking drugs: a review. *Postgrad Med J* 1976; **52**: 63–69.
18. Palmer KN. Respiratory side effects of beta blockers. *Br Med J* 1977; i: 841.
19. Maseri A, Severi S, De Nes M, et al. "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischæmia. Pathogenic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Am J Cardiol* 1978; **42**: 1019–35.
20. Weinev L, Kasparian H, Duca PR, et al. Spectrum of coronary arterial spasm: clinical, angiographic and myocardial metabolic experience in 29 cases. *Am J Cardiol* 1976; **38**: 945–55.
21. Parodi O, Maseri A, Simonetti I. Management of unstable angina at rest by verapamil: a double blind cross-over study in coronary care unit. *Br Heart J* 1979; **41**: 167–74.
22. Neumann M, Luisada AA. Double blind evaluation of orally administered iproveratril in patients with angina pectoris. *Am J Med Sci* 1966; **251**: 552–56.
23. Sandler G, Clayton GA, Thornicroft SG. Clinical evaluation of verapamil in angina pectoris. *Br Med J* 1968; iii: 224–27.
24. Bala Subramanian V, Khanna PK, Narayanan GR, Hoon RS. Verapamil in ischæmic heart disease—quantitative assessment by serial multistage treadmill exercise. *Postgrad Med J* 1976; **52**: 143–47.

"Measurement and logic are 'general' methods found in all sciences, in varying qualities. Measurement has been particularly important in enabling science to expand human images of the world beyond the human scale toward the very large (for instance, in cosmology) or toward the very small in the molecule of the atom, the proton, electron, and now even smaller elementary structures. Measurement is a function of technology, and it could well be, indeed that technology has contributed more to science historically than science has to technology. There is at least a constant feedback between them. Measurement is important in testing, especially as we move beyond the human scale. The Michelson-Morley experiment on the velocity of light only established that this was constant within the range of measurement. If the range of measurement had been, say, 10 percent of the velocity, the experiment would not have been very conclusive."—K. E. Boulding. Science: our common heritage. *Science* 1980; **207**: 831–36.

SOMATOSTATIN AND CIMETIDINE IN PEPTIC-ULCER HÆMORRHAGE

A Randomised Controlled Trial

L. KAYASSEH, K. GYR, U. KELLER, G. A. STALDER, M. WALL

Division of Gastroenterology, Kantonsspital Basle and Hoffmann-La Roche, Basle

Summary In a randomised controlled trial somatostatin was compared with cimetidine in the treatment of severe and persistent gastrointestinal bleeding due to peptic ulcer. The study was of a sequential design and lasted 2·5 years, when the designated level of significance had been reached. Of the 20 patients studied, 10 received somotostatin and 10 received cimetidine. In 7 of the 10 pairs of patients somatostatin was more effective than cimetidine; in 2 pairs somatostatin and cimetidine were both ineffective; and in 1 pair they were equally effective. Somatostatin may therefore be suitable for controlling peptic-ulcer bleeding in many patients who are unsuitable for surgery.

Introduction

SOMATOSTATIN is a potent inhibitor of test-meal and pentagastrin-stimulated gastric acid[1] and pepsin secretion,[2] as well as of gastrin release.[1] By exerting an inhibitory effect on these ulcerogenic factors, somatostatin could influence the development and promote healing of peptic ulcer. Indeed, somatostatin helps to prevent stress ulcers in rats,[3,4] and can also substantially reduce splanchnic blood-flow.[5,6]

Several features therefore make it a potential candidate for the control of hæmorrhage due to peptic ulcer. In a pilot study, somatostatin was effective in the treatment of gastroduodenal hæmorrhage.[7] We compared the efficacy of somatostatin in the treatment of patients with severe gastrointestinal bleeding due to peptic ulcer with that of cimetidine, which is effective in the treatment of bleeding erosions and ulcers.[8,9]

Patients and Methods

Patients

Patients with severe persisting acute hæmorrhage (requiring more than 3 units of blood/24 h), chronic oozing (which required more than 2 units of blood/24 h), or recurrent bleeding (more than twice in 24 h) caused by peptic ulcer and verified by endoscopy were admitted to the study. The hæmorrhage had to be such that it did not cease spontaneously and had been resistant to conservative treatment with gastric ice-water lavage, antacids, and blood-transfusions for at least 4 h. Only patients unsuitable for emergency surgery because of age, concomitant disease, or bad general health were included in the study; normally surgery would have been indicated in every situation.

All patients (or when necessary, their relatives) gave their informed consent for participation in the study.

Study Design and Statistical Analysis

Patients were selected at random for two treatment schedules by a sequential statistical design:

1. Somotostatin—infusion of 250 μg/h for 48–120 h[7] after an intravenous bolus injection of 250 μg by an infusion pump.
2. Cimetidine—intravenous injection of 200 μg every 4 h for 48–120 h.[10]

All patients had a gastric tube and received intravenous fluids, electrolytes, plasma expanders, and blood-transfusions when needed, to keep the circulation stable. The basic electrolyte

solution contained 25 g/l of glucose. No antacids were allowed during the trial. Blood pressure, pulse rate, breathing rate, urinary output, and gastric aspirates were monitored continuously or at regular intervals.

The need for continuing the drug treatment was assessed by gastric lavage with ice-water performed at least every hour and by monitoring the parameters of blood-circulation. Treatment with somatostatin or cimetidine was continued for at least 48 h (but not more than 120 h) and was considered successful when the gastric aspirate had remained clear for 24 h with therapy. The cessation of bleeding was confirmed in each case by endoscopy, up to 12 h after the end of the trial drug treatment. The degree of success was assessed from the number of blood-transfusions before and during therapy. Hæmoglobin concentration white blood-cell count, thrombocytes, prothrombin-time and blood-glucose were determined every 12 h; electrolyte and creatinine levels were measured at least once a day; and liver function, urine output, and coagulation factors assessed before and after treatment.

A sequential analysis[11] was chosen so that the minimum number of patients would be needed to give a statistically significant result as soon as possible. The trial was controlled with randomised matched pairs but was not double-blind since the almost immediate and complete inhibition of gastric secretion by somatostatin would have been noted from the gastric aspirates, thus breaking the blindness.

Patients were paired according to time of entry into the study. Pairs in which both patients had the same result were not taken into account. The trial design gave a predetermined two-sided significance level of 5%.

The trial started in February, 1977, and was completed in August, 1979. 20 patients were admitted to the trial: 10 were treated with cimetidine and 10 with somatostatin.

Results

Before treatment the two groups were well matched for age, sex, source of bleeding, and hæmoglobin concentration (9·6±1·2 g/100 ml in the somatostatin group and 9·4±2·0 g/100 ml in the cimetidine group; mean±SD).

In 7 of the 10 pairs of patients somatostatin was more effective than cimetidine, and in no pair did the reverse occur (see accompanying table). 3 pairs were tied: in 2 pairs somatostatin and cimetidine were both ineffective and in 1 pair they were equally effective. When the 5% level of significance was reached the results favoured somatostatin—i.e., bleeding stopped in 8 out of 10 patients treated with somatostatin but in only 1 treated with cimetidine. Patient 5 rebled 24 h after somatostatin treatment had ended and responded to a second course of somatostatin. In another patient (patient 7) hæmorrhage stopped but restarted under somatostatin treatment; proximal selective vagotomy was performed. In patient 17, the anastomotic ulcer was oversewn and vagotomy performed after failure of somatostatin.

3 of the 9 patients who did not respond to cimetidine treatment died. 1 could not be operated on soon enough because of the seriousness of bleeding (patient 18) and 2 were unsuitable for surgery owing to their bad general condition—patient 9 had decompensated cirrhosis of the liver and patient 1 had metastatic carcinoma of the urinary tract. Among the other 6 patients, 3 underwent proximal selective vagotomy (patients 8, 14, 20) and 1 truncal vagotomy (patient 16). In the other 2 patients bleeding ceased spontaneously some time after therapy with cimetidine ended.

Both groups required the same number of blood-transfusions before treatment began (somatostatin: 4·1±2·2 units, cimetidine: 3·1±1·4 units) but during treatment those treated with somatostatin required significantly fewer (2·0±1·2 units) than those treated with cimetidine (4·7±2·4 units) (Wilcoxon test $p<0.05$). The duration of treatment with cimetidine (54·8±32·2 h) was significantly shorter than that with somatostatin (85·1±37·4 h) (Wilcoxon test $p<0.05$) which reflected the larger number of failures with cimetidine treatment necessitating further therapeutic measures.

No biochemical changes noted during treatment could be attributed to either drug and there were no side-effects apart from the almost total inhibition of gastric secretion with somatostatin.

EFFECT OF TREATMENT

Patient	Age	Sex	Source of bleeding	Effect of treatment: Somatostatin	Effect of treatment: Cimetidine
1	77	M	Duodenal ulcer		failure; died
2	69	M	Gastric ulcer	stopped	
3	78	M	Gastric ulcer		stopped
4	74	M	Duodenal ulcer	stopped	
5	65	M	Stress ulcer	stopped	
6	65	F	Gastric ulcer 10 days after truncal vagotomy		failure
7	65	F	Gastric ulcer 14 days after truncal vagotomy	failure; surgery	
8	78	M	Duodenal ulcer		failure; surgery
9	63	M	Gastric ulcer		failure; died
10	73	F	Duodenal ulcer/ gastric ulcer	stopped	
11	84	F	Gastric ulcer		failure
12	80	M	Duodenal ulcer	stopped	
13	27	M	Duodenal ulcer after truncal vagotomy	stopped	
14	47	M	Duodenal ulcer		failure; surgery
15	78	M	Gastric ulcer	stopped	
16	73	M	Gastric ulcer after gastrojejunostomy		failure; surgery
17	64	M	Anastomotic ulcer after Billroth-II resection	failure; surgery	
18	71	M	Duodenal ulcer		failure; died
19	48	M	Duodenal ulcer	stopped	
20	44	M	Duodenal ulcer		failure; surgery

Discussion

Any study of the control of upper-gastrointestinal hæmorrhage due to peptic ulcer has to acknowledge the fact that most gastrointestinal bleeding stops spontaneously.[12] Meaningful trials can therefore only be conducted with patients whose bleeding would be most unlikely to cease spontaneously. We tried to compare the efficacy of cimetidine and somatostatin in patients with gastric and duodenal ulcers who were most likely to con-

tinue bleeding. Strict selection criteria were applied which were largely consistent with the prognostic signs indicating higher morbidity rates in bleeding patients.[12]

With somatostatin bleeding stopped in 8 out of 10 patients, whereas cimetidine controlled hæmorrhage in only 1 out of 10 patients. These patients were in the higher age-range: 16 out of 20 patients were over 60 years—a group in which operation is indicated whenever possible.

Reports of the failure of cimetidine to control peptic-ulcer bleeding are becoming more common. In a controlled trial Pichard et al[13] noted rebleeding in 8 out of 17 patients with duodenal and gastric ulcers treated with cimetidine and in 8 out of 23 patients treated with placebo. Hoare et al[14] found that cimetidine had no effect on the rebleeding rate in patients with bleeding duodenal ulcers, whereas it had a positive effect in bleeding gastric ulcers. Our controlled trial, however, shows that somatostatin stops ulcer bleeding; this has previously only been postulated in case reports and uncontrolled studies.[3,7,10,15,16] Somatostatin could therefore be used as conservative treatment of persistent peptic-ulcer bleeding in high-risk patients when emergency surgery is indicated but is associated with a high mortality rate,[12] and when stabilisation of the circulation and patient's general condition will decrease the risk of later surgery.

Cyclic somatostatin was kindly donated by Dr Harrant Serrono, Freiburg/Breisgau, West Germany, and cimetidine came from Smith, Kline and French, West Germany.

This study was supported in part by the Swiss National Foundation for Scientific Research, grant no. 3.816 – 0.76.

Requests for reprints should be addressed to L. K., Kantonsspital Basle, CH–4031 Basle, Switzerland.

REFERENCES

1. Bloom SR, Mortimer Ch, Thormer MO, et al. Inhibition of gastrin and gastric acid secretion by growth-hormone release-inhibiting hormone. *Lancet* 1974; ii: 1106–09.
2. Gomez-Pan A, Reed JD, Albinus M, et al. Direct inhibition of gastric acid and pepsin secretion by growth-hormone release-inhibiting hormone in the cats. *Lancet* 1975; i: 888–90.
3. Mattes P, Lauterbach HH, Raptis S, et al. Prevention of stress ulcer by somatostatin in rats. *Langenbecks Arch Chir* 1976; **341**: 297–301.
4. Zierden E, Hengst K, Wagner H, et al. Inhibition of stress ulcer formation with Somatostatin in rats. *Res Exp Med* 1976; **168**: 199–201.
5. Wahren J, Felig Ph, et al. Influence of somatostatin on carbohydrate disposal and absorption in diabetes mellitus. *Lancet* 1976; ii: 1213–16.
6. Keller U, Sonnenberg GE, Kayasseh L, et al. Effect of therapeutic of somatostatin on splanchnic bloodflow in man. *Europ J Clin Invest* 1978; **8**: 335 (abstr.).
7. Kayassch L, Gyr K, Stalder GA, et al. Somatostatin in acute gastroduodenal haemorrhage. *Lancet* 1978; ii: 833.
8. MacDonald AS, Steele BJ, Bottomley MG, et al. Treatment of stress-induced upper gastrointestinal haemorrhage with Metiamid. *Lancet* 1976; i: 68–70.
9. MacDougall BRD, Bailey RJ, Williams R, et al. H_2-Receptor antoganists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminate hepatic failure. *Lancet* 1977; i: 617–19.
10. Gyr K, Kayasseh L, Meyer FD, et al. Somatostatin and cimetidine in gastroduodenal haemorrhage. Proceedings of an international symposium on Histamine H_2-receptor antagonists. Amsterdam Excerpta Medica, 1978: 299–303.
11. Armitage P, et al. Sequential Medical Trials. 2nd ed. Oxford: Blackwell Scientific, 1975.
12. Da Gilbert O, Silverstein FE, Tedesco FJ, et al. Prognosis of upper gastrointestinal bleeding—preliminary results of the ASGE national bleeding survey. *Gastroenterology* 1979; **76**: 1138 (abstr.).
13. Pichard RG, Sonderson I, South M, et al. Controlled trial of Cimetidine in acute upper gastrointestinal bleeding. *Br Med J* 1979; i: 661–62.
14. Hoare AM, Bradby GvH, Hawkins CF, et al. Cimetidine in bleeding peptic ulcer. *Lancet* 1979; ii: 671–73.
15. Brunner H, Panser G, et al. Somatostatin in der Behandlung der akuten Ulcusblutung. *Wiener Klin Wschr* 1978; **13**: 468–71.
16. Bauer H, Doemicke A, Holle F, et al. Prevention and treatment of upper gastrointestinal haemorrhage with cimetidine and somatostatin in intensive care patients. *Anaesthetist* 1977; **26**: 662–64.

EFFECT OF HIGH HÆMATOCRIT ON ALERTNESS

J. R. WILLISON, D. J. THOMAS, G. H. DU BOULAY, JOHN MARSHALL, E. A. PAUL, T. C. PEARSON, R. W. ROSS RUSSELL, L. SYMON, G. WETHERLEY-MEIN

Institute of Neurology, National Hospital, Queen Square, London WC1N 3BG, and St. Thomas' Hospital, London SE1 7EH

Summary Patients with high-normal or above-normal hæmatocrit were found to have impaired alertness when compared with a control group matched for age and occupation. On retesting the controls had improved alertness scores attributable to a practice effect; but the patients, when retested after reduction of hæmatocrit by venesection, had improved significantly more than the controls. Improvement in alertness correlated very well with the increase in cerebral blood flow which followed venesection. Levels of venous hæmatocrit that are generally accepted as normal may not necessarily be optimum.

Introduction

PATIENTS with high blood viscosity may feel "thick-headed" and lethargic. This occurs either with high plasma viscosity resulting from dysproteinæmia[1] or with high whole-blood viscosity due to a high venous hæmatocrit (VH).[2,3]

Cerebral blood flow (CBF) has been found to be low in patients with high-normal or marginally elevated VH (>0·46) and to improve on therapeutic venesection.[4] It has been argued that low CBF associated with raised VH is simply a physiological consequence of increased oxygen-carrying capacity.[5] If this were so performance on psychological tests should not be affected by a high VH and lowering it should not lead to an improvement in performance. Our aim in the present study was to discover whether patients with high viscosity and low CBF due to a high-normal or elevated VH had impaired performance on objective psychological tests, and, if so, whether this deficit improved with treatment.

Patients and Methods

The patients were 23 men and 1 woman whose VH had been found to exceed 0·46 on routine hæmatological investigation. The mean VH was 0·534 (range 0·460 to 0·77). Their mean age was 55·3 years (range 26 to 75). Median occupational status, graded according to the Census classification,[6] was 2·75. No patient was included in whom there was any evidence of a neurological condition which might have impaired his ability to perform psychological tests. The control subjects were 27 men and 7 women, mainly hospital personnel, with no known medical, neurological, or blood disorder. Their mean age was 54·0 years (range 33 to 74) and median occupational level 2·82.

Patients with untreated hypertension have shown deficits in speed of reaction, but not in more specific cognitive skills, compared with control subjects.[7,8] Since our patients were not complaining of any difficulty with memory or other higher cortical function, we chose tests which emphasised speed and accuracy of performance. Four such "alertness" tests were assembled from a variety of sources: